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Magnetic Resonance Imaging Estimation of Longitudinal Relaxation Rate Change (R_1) in Dual Gradient Echo Sequences Using an Adaptive Model

H. Bagher-Ebadian, S. P. Nejad-Davarani, M.M. Ali, S. Brown, M. Makki, Q. Jiang, D.C. Noll, and J. R. Ewing

Physics Dept., Oakland University, Rochester, MI 48309 and Dept. Nuclear Engineering, Shiraz University, Shiraz; Siamak P. Nejad-Davarani – Dept. Neurology, Henry Ford Hospital and Dept. Biomedical Eng. University of Michigan, Ann Arbor; Meser M. Ali - Dept. Radiology, Henry Ford Hospital, Stephen L. Brown - Dept. Radiation Oncology, Henry Ford Hospital, Malek Makki, - Dept. Diagnostic Imaging, University Children Hospital of Zurich, Zurich, Switzerland, Quan Jiang - Dept. Neurology, Henry Ford Hospital; Douglas. C. Noll - Dept. Biomedical Engineering, University of Michigan, Ann Arbor, James R. Ewing Dept. Neurology, Henry Ford Hospital, Dept. Neurology, Wayne State University., and Dept. of Physics, Oakland University

Abstract

Magnetic Resonance Imaging (MRI) estimation of contrast agent concentration in fast pulse sequences such as Dual Gradient Echo (DGE) imaging is challenging. An Adaptive Neural Network (ANN) was trained with a map of contrast agent concentration estimated by Look-Locker (LL) technique (modified version of inversion recovery imaging) as a gold standard. Using a set of features extracted from DGE MRI data, an ANN was trained to create a voxel based estimator of the time trace of CA concentration. The ANN was trained and tested with the DGE and LL information of six Fisher rats using a K-Fold Cross-Validation (KFCV) method with 60 folds and 10500 samples. The Area Under the Receiver Operator Characteristic Curve (AUROC) for 60 folds was used for training, testing and optimization of the ANN. After training and optimization, the optimal ANN (4:7:5:1) produced maps of CA concentration which were highly correlated ($r = 0.89$, $P < 0.0001$) with the CA concentration estimated by the LL technique. The estimation made by the ANN had an excellent overall performance (AUROC = 0.870).

I. Introduction

Magnetic Resonance imaging (MRI) plays a central role in quantification and diagnosis of cerebral pathologies such as ischemia and solid tumor [1]. Dynamic Contrast Enhanced (DCE) and Dynamic Susceptibility Enhanced (DSC) techniques in MR imaging provide useful information about tissue characteristics, anatomy, and functionality. In DCE-MRI, T_1 -weighted images are serially acquired during the intravenous administration of paramagnetic contrast agents (CAs)[1–3], thus allowing these T_1 -effective compounds to be used as indicators to study vascular physiology, particularly Blood Brain Barrier (BBB)

permeability [4–6]. MR measurement of CA concentration can quantify kinetic model parameters such as K^{trans} (transfer rate), PS (microvascular permeability-surface area product), cerebral blood volume (CBV), and cerebral blood flow (CBF); these in turn can be used as markers for classifying cerebral pathologies [4, 6]. A common assumption is that the relationship between the change in longitudinal relaxation rate R_1 ($R_1=1/T_1$) and CA concentration in tissue is linear [7]. However, nonlinearities in the MR measurement of R_1 due to limited access of water in tissue compartments distal to the CA can substantially bias estimates of tissue CA concentration. In addition to the non-linearity problem, in fast MR sequences, the T_2^* contrast competes with T_1 contrast and can bias the estimate of T_1 [8].

The Look-Locker (LL) pulse sequence is an inversion recovery imaging technique offering an unbiased estimation of longitudinal relaxation time (T_1); it shows no evidence of bias in its estimates of tissue CA concentration [9–11]. However, LL imaging is classified as a slow imaging technique due to the time required for full recovery of the longitudinal magnetization between sequential inversion pulses. On the other hand, the Dual Gradient Echo (DGE) pulse sequence is a fast imaging technique with short echo time and relatively short time interval between image acquisitions (2 to 4 sec). DGE imaging allows computation of T_1 and T_2^* as pure components: this is essential for estimation of CA concentration (R_1 and R_2^*). However, in practice the complex relationship between signal intensity, T_1 , T_2^* , and other model parameters such as M_0 and flip angle, makes the dynamic estimation of R_1 in the presence of noise levels typical of MRI, quite challenging.

Herein, we hypothesize that, given DGE data as a basis set, a time trace of CA concentration, could be estimated by an Adaptive Neural Network (ANN) trained by the CA concentration map produced from the LL technique (gold standard of training).

In this study an adaptive neural network (ANN) was trained by LL sequences to estimate CA concentration from a set of features extracted from a DGE pulse sequence. The output of the ANN was in units of R_1 as measured by a LL sequence; *i.e.*, since the LL measure of R_1 is approximately linear in CA concentration, the output of the ANN was proportional to the concentration-time trace of the tissue concentration of CA, independent of tissue and other factors.

MATERIALS AND METHODS

A. Hypothesis

In this study it was hypothesized that an ANN could be trained by a set of features extracted from DGE signals as its input and a map of CA concentration produced by the LL method as its output. The perfected ANN can be used to estimate the concentration-time curve of CA concentration (LL- R_1) in the DGE experiment.

B. Animals and Tumor Pathology

Six Fisher rats (Female, 0.150 Kg) were implanted with U251n tumor (Orthotopic tumor). MR images were acquired for training and testing the ANN. All animal experiments were performed according to the NIH guideline, with a protocol approved by the Henry Ford Health System animal care and user committee (IACUC). For obtaining U251n tumor cells,

human Glioma cells were cultured in Dulbecco's modified Eagles medium (DMEM) supplemented with 10% fetal bovine serum (FBS) in 5% CO₂/95% air at 37°C in a humidified incubator. For implantation in rat brain, cells were harvested and re-suspended at a concentration of 8×10^7 per ml of serum free media. At the last stage, 5 μ L of the cell suspension was implanted into the rat brain. At the time of imaging, mean tumor age was 23.4 ± 0.8 days (range 19 to 25 days) for all animals. All animals were anesthetized during the MR experiment using Isoflurane (3.5% for induction, 0.7% to 1.5% maintenance).

C. MR Imaging

Animal imaging was conducted in a 7 Tesla MRI system with a Bruker Avance console running Paravision Version 3.0.2. RF coils were a Bruker volume resonator for transmission, and an actively-decoupled 2 cm Bruker surface coil for reception. All images were taken with a 32 mm FOV. High resolution T₁-weighted images were acquired before and after CA administration and a High-resolution T₂ image set ($T_R/T_E = 2000/10$ ms, matrix 256×192, Seventeen 0.5 mm slices, 4 accumulations) was acquired before CA administration.

Look-Locker Imaging—After a nonselective adiabatic inversion, 24 echoes per phase step at 50 ms intervals, tip-angle (θ) $\sim 18^\circ$, for a total of about 1.2 sec per inversion-recovery line were gathered. T_R (inversion-to-inversion) was approximately 2200 ms. Image matrix was 128×64, 3 slices of 2 mm. This takes about 2.5 minutes per image set [9].

Dual Gradient Echo Imaging—The DGE study consisted of 150 time points with two gradient echoes at 3.4 and 6.8ms, flip angle of 18° and T_R of 60ms. 3 slices of 2 mm thickness were acquired with an image matrix of 128×64. The time needed for acquiring each image pack was around 4 seconds.

Dynamic Study—Fig. 1 shows the order of imaging for the dynamic study. As shown in this figure, in each dynamic study, three sets of MR images were acquired for each animal: 1- two initial pre-injection LL image sets 2- one set of DGE images and 3- two post-injection LL sets. Gd-DTPA was intravenously injected as a bolus (140 μ mol/Kg in about 4 sec) at time 44 sec after the start of the DGE sequence.

D. Theory—Equations (1) and (2) show the first and second signals in DGE pulse sequence:

$$^1_n S = M_0 \sin \theta \left(1 - \cos \theta e^{-\frac{T_R}{T_1}} \right) e^{-\frac{T_{E1}}{T_2^*}} \quad (1)$$

$$^2_n S = M_0 \sin \theta \left(1 - \cos \theta e^{-\frac{T_R}{T_1}} \right) e^{-\frac{T_{E2}}{T_2^*}} \quad (2)$$

where ^1S and ^2S are the first and second echoes respectively. n denotes experiment time points ($n=1$ to 150), θ is the flip angle, T_R the repetition time, T_{E1} and T_{E2} refer to the first and second echo times, M_0 is the magnetization, T_1 represents longitudinal relaxation time,

and T_2^* is the transverse relaxation time with the field inhomogeneity effects. Equations (3) and (4) can be derived from (1) and (2) to extract R_1 and R_2^* components individually:

$$R_1 = -\frac{1}{T_R} \ln \left[\frac{1}{\cos\theta} - \left(\frac{1}{M_0 \sin\theta \cos\theta} \right) \frac{1_n S^{(\frac{T_{E2}}{T_{E2}-T_{E1}})}}{2_n S^{(\frac{T_{E1}}{T_{E2}-T_{E1}})}} \right] \quad (3)$$

$$R_2^* = -\frac{1}{T_{E1} - T_{E2}} \ln \left[\frac{1_n S}{2_n S} \right] \quad (4)$$

Equations 1 to 4 suggest a set of features (μ_1, μ_2, μ_3 , and μ_4), detailed in equations 5 through 8, that are insensitive to system gain and physically meaningful based on the measureable parts of (3) and (4):

$$\mu_1 = \frac{\Delta H_1}{H_1(Pre)} \quad (5)$$

$$\mu_2 = \frac{\Delta H_2}{H_2(Pre)} \quad (6)$$

$$\mu_3 = -\frac{\Delta H_1}{H_1(post)} \ln \left[\frac{1_n S}{2_n S} \right] \quad (7)$$

$$\mu_4 = -\frac{\Delta H_2}{H_2(post)} \ln \left[\frac{1_n S}{2_n S} \right] \quad (8)$$

Where H_1, H_2, H_1 , and H_2 are defined as follows:

$$H_1 = -\frac{1}{T_R} \ln \left[\frac{1_n S^{(\frac{T_{E2}}{T_{E2}-T_{E1}})}}{2_n S^{(\frac{T_{E1}}{T_{E2}-T_{E1}})}} \right] \quad (9)$$

$$H_2 = -\frac{1}{(T_{E1} - T_{E2})} \ln \left[\frac{1_n S}{2_n S} \right] \quad (10)$$

$$\Delta H_1 = H_1(Post) - H_1(Pre) \quad (11)$$

$$\Delta H_2 = H_2(Post) - H_2(Pre) \quad (12)$$

Pre and *post* notations in (11) and (12) denote before and after CA administration.

E. ANN Architecture, Training, and Input

The features (μ_1 , μ_2 , μ_3 , and μ_4) introduced in Equations 5 to 8 were used as the input vector to a feed forward multilayer perceptron (MLP) with back propagation training algorithm. Fig. 2 shows the ANN architecture used in this study. As shown in this figure, the layers of the ANN are divided into the input layer, hidden layer and the output layer. The ANN was trained in a supervised mode, using the back propagation learning algorithm [12–14].

During the training phase, the internode weight adjustment was controlled by the momentum and learning rate factors. For every input vector, the calculated output was compared to the class identifier (training set), which is the value of R_1 created from the LL sequence before and after the CA administration.

In this study, we used the Mean Square Error (MSE) between the output of the ANN and the training set as the measure of error and this value was calculated across all the data set. The weight changes obtained from each training case were accumulated, and the weights updated after the entire set of training cases was evaluated. In order to improve stability and convergence rate for the training set, we used batch processing; however, it should be noted that batch processing improves stability, but with a tradeoff in the convergence rate [12, 15].

Features extracted from the last part (the last 8 sets of DGE echoes when CA concentration in the tumor and vascular bed is approximately constant), and the 3rd through the 10th set of echoes (first part) before CA bolus injection, were averaged and presented to the feature extractor system. The ANN was trained to a small value ($\sim 10^{-5}$) for the first part (before CA injection), and the actual R_1 change estimated by the LL for the last part. A K-fold cross validation (KFCV) method was employed for training, testing, and network optimization [15, 16]. The ANN was trained and validated using KFCV (K-fold Cross Validation) method, also optimized by maximizing the Area Under Receiver Operator Characteristic (AUROC) Curve [16]. 10500 samples from six animals with 60 folds and 175 samples in each randomly split fold were used in the optimization and validation. The optimal architecture for this ANN was found as 4:7:5:1.

F. ANN Optimization and Generalization Error

To construct a generalized ANN (to allow its application to a wide range of inputs), it is important to avoid both under-fitting (which generates a high variance in the output estimate) and over-fitting (which produces biased outputs) of the training data. The strategies stated below guarantee the ANN generalization:

1. Optimizing the number of free parameters (independent connection weights) in the model (e.g., the number of neurons in each layer and the number of layers).
2. Stopping the gradient descent training at an appropriate point (avoid over fitting).
3. Adding noise to the training patterns to smear up the data points.

Usually strategy number 3 is recruited in cases where local minima “trap” the ANN optimization process. Strategy number 3 was not used in this study since no trapping was observed during the training phase. To employ strategies number 1 and 2, it was crucial to estimate from our training data what the generalization error was likely to be. To

characterize the generalization error, we trained and validated the ANN by the KFCV method using the area under the receiver operator characteristic (AUROC) curve as a cost function [15, 17–19]. In KFCV, the training data are divided randomly into K distinct subsets; the network is then trained using K-1 subsets, and tested on the remaining subset. The process of training and testing is then repeated for each of the K (K=60) possible choices of the subset omitted from the training. In our case, to have a more uniform sampling in each fold, the KFCV was repeated 100 times, and every time, the whole training data was randomly split into 60 folds for training and cross-validation. The average Correct Classification Fraction (CCF) at different epochs for K omitted subsets were plotted, and the epoch corresponding to 10% of its plateau was taken to be the stopping epoch. The mean squared error (MSE) of the ANN for all K subsets at their different epochs was calculated and the average value of the MSE at the stopping epoch was taken as the measure of generalization error. This procedure has the advantage that it allows us to use a high proportion of the available training data, *i.e.* $(1 - 1/K)$ of the entire dataset, for training, while making use of all the data points in estimating the generalization error or agreement. The cost is that the process can be time consuming, since we need to train and evaluate the network K times.

Typically, $K \sim 10$ is considered reasonable [16, 17]. In this study, K was set to 60 for 6 animals (175 samples in each fold) and the ANN had a single output, to predict the CA concentration at different time points.

To measure how accurately this ANN estimated the CA concentration for the entire dataset, as shown in Fig. 3, the ANN's CCF curve was generated at different levels of epochs during the KFCV procedure. The Area Under Correct Classification Fraction (AUCCF) which is proportional to AUROC (Az) value, was used as an index to estimate the ANN's performance, to determine the optimal architecture of the ANN, and also to find the ANN termination error [17, 19]. Each KFCV set was trained until its error was below a defined termination error (*i.e.*, the point at which the training procedure was stopped). The termination error was set by determining the error at the 10% point of the CCF's plateau.

The number of hidden layer nodes may affect the performance of the ANN classifier [16–18]. Since the ANN could not be trained by less than 3 neurons in its first hidden layer, layer and node optimization were done by maximizing the AUCCF value for its second hidden layer as a function of the number of nodes.

In the ANN the internal activation function of its neurons is a sigmoid function that is most easily programmed to work in a polar mode between - 1 and 1; the one output neuron has a unipolar saturated function with a range from 0 to 1.0. In order to present an easily understood comparison, the response of the trained ANN for the saturation part of the DGE experiment was compared to the CA concentration maps estimated from the LL (gold standard) by calculating a correlation coefficient using all of the pixel comparisons available and ROC curve of the optimal ANN. The AUROC reported in Fig. 3 was generated based on the KFCV and Leave-One-Out method. In this method, the data is not divided into a fixed training and testing subsets; every fold is used in training and testing stages and for each ANN structure a cumulative score is measured from the combination of the KFCV and

Leave-One-Out techniques at the plateau of the CCF [15, 16, 18, and 19]. The average MSE at the stopping point (10% of plateau) for the optimal structure was around 1.7×10^{-8} .

In this study since the output of the ANN is not binary and produces continuous values of relaxivity change, to test and validate the ANN accuracy against the map of relaxivity change in Look-Locker (Gold Standard of training), the minimum acceptable error for the relaxivity change was calculated based on an error propagation technique using minimum acceptable errors of ± 10 ms for the pre and post injection T_1 values. Therefore the values of the ANN output and the relaxivity change constructed from the LL map both were broken down into discrete fragments using a small bin ($2 \times 10^{-5} \text{ ms}^{-1}$) in the phase of KFCV validation and training.

II. RESULTS

As shown in Fig. 3, the optimal architecture (4:7:5:1) of the ANN was found at an AUROC of 0.870. The trained ANN (4:7:5:1) was applied to the DGE images of the six animals to generate a time course of R_1 maps, including the pre and post injection time points.

Fig. 4 shows a set of R_1 maps in tumor and normal areas for one of the animals, generated by the trained ANN for all time points (0~600 sec) before and after CA administration. This figure illustrates the extravastation of CA concentration at different time points after CA administration. The plots in Fig. 5 illustrate the trained ANN's estimate of the time courses for R_1 in the normal (blue) and tumor (red) zones, along with the gold standard value of the R_1 (average in tumor: $3.578 \times 10^{-3} \text{ sec}^{-1}$) estimated from LL data. As shown in this figure, the R_1 (at the final time point ~ 600 sec) estimated by the ANN for the tumor area (average in tumor: $3.578 \times 10^{-3} \text{ sec}^{-1}$) is highly correlated ($r=0.89$, $p<0.0001$) with the R_1 generated by the LL. Of particular note is the agreement between the ANN estimate of R_1 and the R_1 produced from the LL technique. Fig. 6 illustrates brain histology, T_1 -weighted high resolution image after injection, CA concentration map generated by LL technique, and CA concentration map estimated by the trained ANN at time 600 sec after injection. As shown in this figure, the tumor area is quite heterogeneous with a necrotic core, in agreement with the CA concentration map estimated by the trained ANN at time 600 sec.

III. DISCUSSION

An ANN was trained, optimized and evaluated using KFCV technique to construct a CA concentration estimator from DGE pulse sequence. The perfected ANN was applied to DGE pulse sequences at different time points (before and after CA administration) to produce a voxel based time trace of CA concentration. Although the ANN was trained only by the features extracted from the beginning and final time points of the DGE pulse sequence, the trained ANN was able to estimate the time trace of CA concentration at all the time points. Results imply that the trained ANN can estimate CA concentration quantitatively across time.

The number of operations needed for the trained ANN to produce the CA concentration for a voxel from a set of extracted feature set is about 68. This is much less than the many thousands of operations required in the iterative and multidimensional non-linear fitting

techniques used in similar pulse sequences for estimating the CA concentration; a time trace of R_1 maps (150 time points) with dimension of 128×128 can be estimated by the trained ANN in less than three minutes on a computer with a 2.2 MHZ CPU.

A fast and robust estimator of CA concentration from fast pulse sequences such as DGE raises the possibility of real-time evaluation and generation of hemodynamic maps in permeability and perfusion studies.

The R_1 time course estimated by the trained ANN is stable with a reasonable rise time for CA concentration. The ANN also appears to be generating estimates of R_1 that are close to known values of R_1 in tumorous and normal tissues at 7T. This pilot study demonstrates the feasibility of applying an ANN to the problem of estimating R_1 in fast imaging techniques as a function of time before and after injection of CA.

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References

1. Vonken EP, et al. Simultaneous quantitative cerebral perfusion and Gd-DTPA extravasation measurement with dual-echo dynamic susceptibility contrast MRI. *Magn Reson Med.* Jun.2000 43:820–7. [PubMed: 10861876]
2. Faranesh AZ, Yankeelov TE. Incorporating a vascular term into a reference region model for the analysis of DCE-MRI data: a simulation study. *Phys Med Biol.* May 21.2008 53:2617–31. [PubMed: 18441417]
3. Yankeelov TE, et al. Incorporating the effects of transcytolemmal water exchange in a reference region model for DCE-MRI analysis: theory, simulations, and experimental results. *Magn Reson Med.* Feb.2008 59:326–35. [PubMed: 18228592]
4. Gossman A, et al. Dynamic contrast-enhanced magnetic resonance imaging as a surrogate marker of tumor response to anti-angiogenic therapy in a xenograft model of glioblastoma multiforme. *J Magn Reson Imaging.* Mar.2002 15:233–40. [PubMed: 11891967]
5. Pellerin M, et al. Incorporating contrast agent diffusion into the analysis of DCE-MRI data. *Magn Reson Med.* Dec.2007 58:1124–34. [PubMed: 17969007]
6. Sourbron S, et al. Bolus-tracking MRI with a simultaneous T_1 - and T_2^* -measurement. *Magn Reson Med.* Sep.2009 62:672–81. [PubMed: 19585599]
7. Bagher-Ebadian H, et al. MRI estimation of gadolinium and albumin effects on water proton. *Neuroimage.* Jan; 2011 54(Suppl 1):S176–9. [PubMed: 20493266]
8. Barbier EL, et al. A model of the dual effect of gadopentetate dimeglumine on dynamic brain MR images. *J Magn Reson Imaging.* Sep.1999 10:242–53. [PubMed: 10508283]
9. Gelman N, et al. Interregional variation of longitudinal relaxation rates in human brain at 3.0 T: relation to estimated iron and water contents. *Magn Reson Med.* Jan.2001 45:71–9. [PubMed: 11146488]
10. Paudyal R, et al. MRI Look Locker Estimates of the Longitudinal Relaxation Rate Are Approximately Linear in Contrast Agent Tissue Concentration. *Proc Int Soc Mag Reson Med.* 2008; 17:2305.

11. Paudyal R, et al. The Effects of Equilibrium intercompartmental Water Exchange Kinetics on MRI Estimation of Tissue Concentration of Contrast Agents. *Proc Int Soc Mag Reson Med*. 2009; 17:722.
12. Freeman, JA.; Skapura, DM. *Neural networks : algorithms, applications, and programming techniques*. Reading, Mass: Addison-Wesley; 1991.
13. Gurney, K. *An introduction to neural networks*. London: UCL Press; 1997.
14. McCulloch WS, Pitts W. A logical calculus of the ideas immanent in nervous activity. 1943. *Bull Math Biol*. 1990; 52:99–115. discussion 73–97. [PubMed: 2185863]
15. Looney, CG. *Pattern recognition using neural networks : theory and algorithms for engineers and scientists*. New York: Oxford University Press; 1997.
16. Bishop, CM. *Neural networks for pattern recognition*. Oxford: Oxford University Press; 1997.
17. Bagher-Ebadian H, et al. MRI estimation of contrast agent concentration in tissue using a neural network approach. *Magn Reson Med*. Aug.2007 58:290–7. [PubMed: 17654573]
18. Bagher-Ebadian H, et al. Neural network and fuzzy clustering approach for automatic diagnosis of coronary artery disease in nuclear medicine. *IEEE Transactions on Nuclear Science*. 2004; 51:184–192.
19. Hosseini-Ashrafi ME, et al. Pre-optimization of radiotherapy treatment planning: an artificial neural network classification aided technique. *Phys Med Biol*. Jun.1999 44:1513–28. [PubMed: 10498520]

Fig. 1.

From left to right: two LL series, DGE experiment (150 time points), and two LL series. Tail vein injection of CA concentration is done during the DGE experiment.

Fig. 2.
Optimal ANN (4:7:5:1) architecture.

Fig. 3. Node optimization curve for the second hidden layer of the ANN (with 7 neurons in its first hidden layer).

Fig. 4.

From left to right and top to bottom: ANN estimation of CA concentration at different time points before and after CA administration. The CA concentration map at time of 600 sec (last time point) is highly correlated ($r=0.89$ ($p<0.0001$)) with the CA concentration estimated by the LL technique (see Fig. 5).

Fig. 5.

Estimates of the ANN for the time courses of the R_1 in the normal (blue) and tumor (red) areas, along with the gold standard value of the R_1 calculated by the LL technique. The high resolution post injection T_1 image shows the location and morphology of the tumor in the same slice.

Fig. 6.

From top to bottom left to right: Brain histology and T₁ high resolution image after injection, CA concentration map generated by LL technique, CA concentration map estimated by the trained ANN at time 600 sec after injection.